REMARKS

Claims 1-5, 7-17, and 19-60 are currently pending, with claims 24-60 having been withdrawn from further consideration. By the present communication, no claims have been added or canceled, and claims 1 and 13 have been amended to define Applicants invention with greater particularity. Support for the amended claim language may be found throughout the specification and claims as filed. Upon entry of the present amendment, claims 1-5, 7-17, and 19-23 and will be under consideration.

Priority

Applicants respectfully traverse the Office Action's assertion that the present claims are not entitled to claim the benefit of priority of U.S. Serial No. 60/512,651 (hereinafter "the '651 provisional application"), filed October 20, 2003, and instead are only entitled to claim the benefit of International Application No. PCT/US04/34534, filed on October 20, 2004.

In particular, the Office Action indicates that the provisional application does not specifically mention agonists or antagonists and these terms are broader than the term "inhibitor." In addition, the Office Action indicates that as amended, "the claims now recite cylcopamine, KAAD-cyclopamine, jervine, SANT-1, SANT-2, SANT-3, and SANT-4 and these compounds are not mentioned in the provisional application." Applicants maintain that pages 12-16 of the '651 provisional application are essentially identical to Watkins *et al.* (*Nature* 422:313-317, 2003), which the Examiner has cited in a rejection of claims 1-7 and 13-19 under 35 U.S.C. §102(b). Applicants further maintain that the Examiner's assertion that the claims are anticipated by this reference is an acknowledgment that these claims are supported by the '651 provisional application, which includes the disclosure of Watkins *et al.* in its entirety. However, without acquiescing the reasoning of the Action, and in order further prosecution, Applicants have amended claims 1 and 13 to limit the antagonists to cylcopamine and KAAD-cyclopamine, which are specifically disclosed on page 14 of the '651 provisional application (see *e.g.*, col. 1, first full paragraph on page 14). Accordingly, Applicants submit that, at a minimum, amended

claims 1-7 and 13-19 are entitled to benefit of priority to the filing date of the '651 provisional application.

Rejections Under 35 U.S.C. §102

Applicants respectfully traverse the rejection of claims 1-5, 7, 13-17 and 19 under 35 U.S.C. §102(b) as allegedly being anticipated by Watkins *et al.* (*Nature* 422:313-317, 2003; hereinafter "Watkins") as evidenced by Zhang *et al.* (*Bioorganic Med Chem Lett* 18:1359, 2008; hereinafter "Zhang").

The Office Action alleges that Watkins discloses the use of the steroid alkaloid cyclopamine and KAAD-cyclopamine to inhibit the hedgehog signaling pathway in small cell lung cancer, citing Zhang as evidence that the structure of cyclopamine reads on Applicants' invention. Applicants respectfully submit that Watkins is not available as prior art under 35 U.S.C. §102(b). As discussed above, the present claims are entitled to claim the benefit of priority of the '651 provisional application, filed October 20, 2003. Watkins, which cites a publication date of March 2003, was published less than a year before the priority date. Thus, Watkins fails to meet the standard under 35 U.S.C. §102(b), in which the reference must have been published more than one year prior to the date of the application. Accordingly, Watkins is not available as prior art under 35 U.S.C. §102(b).

As previously discussed, Applicants further submit that Watkins is also not available as prior art under 35 U.S.C. §102(a). According to M.P.E.P. § 715.01(c), where the Applicant is one of the co-authors of a publication cited against his or her application, he or she may overcome the rejection by filing a specific affidavit or declaration under 37 C.F.R. § 1.132 establishing that the article is describing Applicant's own work. An affidavit or declaration by Applicant alone, indicating that Applicant is the sole inventor and that the others were merely working under his or her direction, is sufficient to remove the publication as a reference under 35 U.S.C. § 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

On March 2, 2009, Applicants filed a declaration under 37 C.F.R. § 1.132 by Dr. Philip A. Beachy establishing that Watkins describes the inventors' own work, and indicating that Scott G. Burkholder and Baolin Wang are not inventors in the subject application. Applicants submit

that the declaration filed on March 2, 2009 applies equally and is incorporated here. As such, Watkins is not available as prior art under 35 U.S.C. § 102(a) against the subject application. Withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 1-5, 7-9, 13-17, 19, 20, and 23 under 35 U.S.C. §102(e), as allegedly being anticipated by Dudek *et al.*, US Patent Application Publication No. 2004/0060568 (hereinafter "Dudek"). The Office Action alleges that Dudek teaches methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling pathway. In addition, the Office Action alleges that Dudek teaches hedgehog antagonists including antibodies and cyclopamine.

Applicants respectfully traverse this basis for rejection and submit that Dudek fails to anticipate the presently claimed invention because it does not teach each and every element of the claims. Without acquiescing the reasoning of the Action, and in order to further prosecution, Applicants respectfully submit that the claims have been amended to recite a method of reducing or inhibiting metastasis of small-cell lung cancer (SCLC) cells (see claim 1) and a method of ameliorating small-cell lung cancer in a subject comprising administering to the subject: i) at least one Hh pathway antagonist selected from the group consisting of cyclopamine and KAAD-cyclopamine, and ii) an antibody or binding fragment thereof, wherein the antibody or binding fragment thereof is an Hh pathway antagonist (see claim 13).

The Office Action contends that the Dudek discloses that unusually high levels of Gli-1 levels are treated (and specifically discloses small cell carcinomas in the lung) with hedgehog antagonists as preferred embodiments (0544) and shows data to support this (see Table 2). Applicants respectfully disagree and submit that Dudek merely teaches that 3/6 SCLC samples exhibit Gli-1 expression. Dudek provides no data whatsoever to support the assertion that Shh antagonists are effective in inhibiting metastasis of SCLC cells as presently claimed. Furthermore, Dudek is completely silent with regard to any teaching of ameliorating SCLC in a subject by administering to the subject a combination of small molecule hedgehog antagonists and an antibody that acts as a Hedgehog pathway antagonist. Accordingly, Dudek fails to anticipate the presently claimed invention because it does not teach each and every limitation of the claims. Withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 1-5, 8-17, and 20-23 under 35 U.S.C. §102(e), as allegedly being anticipated by Ling, *et al.*, U.S. Patent Application Publication No. 2005/0054568 (hereinafter "Ling"). The Office Action alleges that Ling teaches methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling pathway. Applicants respectfully disagree and submit that Ling merely teaches that 7/11 lung cancer samples exhibit Gli-1 expression. Ling provides no data whatsoever to support the assertion that Shh antagonists are effective in inhibiting metastasis of SCLC cells as presently claimed. Furthermore, Ling is completely silent with regard to any teaching of ameliorating SCLC in a subject by administering to the subject a combination of small molecule hedgehog antagonists and an antibody that acts as a Hedgehog pathway antagonist. Accordingly, Ling fails to anticipate the presently claimed invention because it does not teach each and every limitation of the claims. Withdrawal of the rejection is respectfully requested.

Double Patenting

Applicants respectfully traverse the provisional rejection of claims 1-7, 13-19, and 23 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 43-75 of co-pending U.S. Serial No. 11/338,503. Specifically, the Office Action alleges that "[t]he person who signed the terminal disclaimer [filed on March 2, 2009] is not recognized as an officer of the assignee and he/she has not been established as being authorized to act on behalf of the assignee." (Office Action, page 9). In addition, the Advisory Action indicates that a new Terminal Disclaimer and a 3.73(b) certificate must be filed.

Attached herewith as Exhibit A is a copy of reel/frame 017763/0671, recorded on June 12, 2006, showing that the co-inventors have assigned all right, title, and interest to the claimed subject matter to The Johns Hopkins University. Attached herewith as Exhibit B is a copy of the Power of Attorney by Assignee filed January 23, 2007 in connection with the instant application, appointing the DLA Piper US LLP attorneys of USPTO Customer No. 28213 to prosecute the Application for the assignee and transact all business in the USPTO connected therewith. Finally, attached herewith is an executed 3.73(b) certificate and a new Terminal Disclaimer

signed by an attorney of record. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections Under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 1-5, 7-9, 11-17, and 19-23 under 35 U.S.C. §103(a) as allegedly being unpatentable over Dudek in view of Chen (PNAS vol. 99 p. 14071; hereinafter, "Chen"). Specifically, the Office Action alleges that Dudek teaches as discussed above and that Chen teach that SANT-1 to SANT-4 have hedgehog pathway inhibitory activities similar to cyclopamine (see page 14074, second column, second full paragraph) and that KAAD-cyclopamine is a potent cyclopamine derivative that is more potent in inhibiting hedgehog activity (page 14072, bottom of first column). The Office Action therefore concludes that in view of Chen, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use SANT-1 to SANT-4 or KAAD-cyclopamine in place of cyclopamine to inhibit small cell lung carcinoma. In addition, the Office Action concludes that the combination of the small molecule antagonist with the antibody is obvious because Dudek discloses that anti-Hh antibodies are effective hedgehog antagonists.

Applicants submit that the Action fails to provide a sufficient rationale for one having ordinary skill in the art to practice the presently claimed invention with any reasonable expectation of success and thus, fails to establish a *prima facie* case of obviousness against the presently claimed invention.

Applicants respectfully submit that Chen fails to remedy the insufficiencies of Dudek and thus, the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention because the references do not teach or suggest each and every element of the claims. "To establish a *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

At a minimum, it must be demonstrated that the cited references provide a sufficient basis to predictably arrive at the presently claimed invention, and even assuming, *arguendo*, that the cited references teach each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation

of success. See *KSR v. Teleflex*, Inc., No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art").

In the instant case, the Action has not provided sufficient rationale to support how the skilled artisan would have combined the methods of the prior art and arrive at the presently claimed methods of reducing or inhibiting metastasis of SCLC or a method of ameliorating SCLC in a subject with any reasonable expectation of success, as alleged in the Action.

The Action asserts that the combination of small molecule and antibody Hedgehog antagonists would be obvious because, "[i]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose .... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846,850,205 USPQ 1069, 1072 (CCPA 1980).

Applicants respectfully disagree and point out that in the instant case, the hedgehog antagonists are administered for the purpose of reducing, inhibiting, or ameliorating SCLC. Applicants respectfully submit that neither Dudek nor Chen nor any art of record teach the use of the presently claimed compounds or an antibody or binding fragment thereof, wherein the antibody or binding fragment thereof is an Hh pathway antagonist for the purpose reducing, inhibiting, or ameliorating SCLC. The Action has not provided a sufficient rationale to establish a nexus between inhibiting the hedgehog pathway and reducing, inhibiting, or ameliorating SCLC. Thus, the skilled artisan would have no reasonable expectation of success in practicing the claimed invention.

The Action has failed to provide sufficient rationale for the skilled artisan to arrive at the presently claimed invention with any reasonable expectation of success. Moreover, Chen fails to remedy the insufficiencies of Dudek. Thus, for at least these reasons, the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 1-5, 8-17, and 20-23 under 35 U.S.C. §103(a) as allegedly being unpatentable over Ling in view of Chen. Specifically, the Office Action alleges that Ling teaches as discussed above and that Chen teach that SANT-1 to SANT-4 have hedgehog pathway inhibitory activities similar to cyclopamine and that KAAD-cyclopamine is a potent cyclopamine derivative that is more potent in inhibiting hedgehog activity.

Applicants submit that the Action fails to provide a sufficient rationale for one having ordinary skill in the art to practice the presently claimed invention with any reasonable expectation of success and thus, fails to establish a *prima facie* case of obviousness against the presently claimed invention.

Applicants respectfully submit that Chen fails to remedy the insufficiencies of Ling and thus, the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention because the references do not teach or suggest each and every element of the claims. "To establish a *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

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Applicants respectfully disagree and point out that in the instant case, the hedgehog antagonists are administered for the purpose of reducing, inhibiting, or ameliorating SCLC. Applicants respectfully submit that neither Ling nor Chen nor any art of record teach the use of the presently claimed compounds or an antibody or binding fragment thereof, wherein the antibody or binding fragment thereof is an Hh pathway antagonist for the purpose reducing, inhibiting, or ameliorating SCLC. The Action has not provided a sufficient rationale to establish a nexus between inhibiting the hedgehog pathway and reducing, inhibiting, or ameliorating SCLC. Thus, the skilled artisan would have no reasonable expectation of success in practicing the claimed invention.

The Action has failed to provide sufficient rationale for the skilled artisan to arrive at the presently claimed invention with any reasonable expectation of success. Moreover, Chen fails to remedy the insufficiencies of Ling. Thus, for at least these reasons, the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

The Commissioner is hereby authorized to charge $650.00 as payment for the Petition for the Two-Month Extension of Time ($245) and the Request for Continued Examination ($405) to Deposit Account No. 07-1896. The Terminal Disclaimer fee of $70.00 was previously paid with the filing of the Terminal Disclaimer on March 2, 2009. No other fees are believed to be due with the present communication, however, the Commissioner is hereby authorized to charge any fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896 referencing the above-referenced attorney docket number.

Respectfully submitted,

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